REMARKS/ARGUMENTS

Claims 2-4, 7, 105, and 106 are canceled without prejudice. Claims 1, 5, 6, 15 and 16 are amended. Claims 1, 5, 6, 8-17, and 22-24 are pending in the application. Reexamination and reconsideration of the application, as amended, are respectfully requested.

Rejection Under 35 U.S.C. § 112:

The Examiner maintained the rejections of claims 15 and 16 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement, because the specification does not provide evidence that the claimed biological materials are deposited. The Examiner noted that the deposit of hybridoma producing antibody FM155 would overcome the rejection with respect to claims 15-16 directed to the monoclonal antibody FM155. Applicants respectfully traverse this rejection.

Claims 15 and 16 have been amended to expressly identify a polypeptide to which antibody FM155 specifically binds. The polypeptide is identified by its sequence SEQ ID NO: 1. Under a recently decided *Noelle v. Lederman*,, 355 F.3d 1343 (Fed. Cir. 2004), the instant specification provides adequate written description and enabling disclosure of the FM155 antibody as claimed in the amended claims 15 and 16. In *Noelle*, the Federal Circuit has summarized the written description requirements with respect to antibodies as follows: "as long as an applicant has disclosed a 'fully characterized antigen,' either by its **structure, formula, chemical name, or physical properties,** or by depositing the protein in a public depository, the applicant can then **claim an antibody by its binding affinity** to that described antigen (*Id.* at 1349, emphasis added). Since the amended claims 15 and 16 expressly identify a polypeptide to which antibody FM155 specifically binds by its sequence, the deposit of FM155 is not required to adequately describe the invention and enable claims 15 and 16.

Claims 1-14, 16-17, 22-24, and 105-106 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. This rejection is moot with respect to claims 2-4, 7, 105, and 106 due to the cancellation of the claims. With respect to claims 1, 5, 6, 8-17, and 22-24, the rejection is traversed.

In spite of a narrow disclosure, an applicant might nonetheless have a written description support for a broader claim if the function and properties of what the applicant disclosed in light of the state of the art indicates to those skilled in the art that the invention is indeed broader. *In re Smythe*, 480 F.2d 1376, 178 U.S. P.Q. 279 (C.C.P.A. 1973). "If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if [not] every nuance of the claims is explicitly described in the specification, then the adequate written description requirement is met." *In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996).

Claim 1 has been amended to limit antagonists of the present invention to those that modify interactions between MMP-9 and β1-containing integrins. Amended claim 1 properly omits unnecessary nuances and focuses on the two key aspects of the present invention: (1) a discovery that MMP-9 binds β1-containing integrins and (2) a discovery that antagonists that modify the interaction of MMP-9 with β1-containing integrin inhibit angiogenesis.

A specification need not "describe the exact details for preparing every species within the genus described." *Staehelin v. Secher*, 24 USPQ2d 1513, 1520 (Bd. Pat. App. & Int'f 1992). In the present invention, the antagonists covered by the claimed genus are characterized by a common functional feature – their ability to modify an interaction between MMP-9 and β1-containing integrins. As discussed on page 6 of the instant specification (lines 11-13) and page 4, lines 10-18, of Melvin, MMP-9 is a 92-kDa enzyme with a well-studied and known sequence and structure. Integrins of β1 subfamily are also well-characterized as they share a common

feature, β1 subunit (page 6, line 29- page 7, line 14). The ability of the antagonists of the present invention to modify binding of MMP-9 and β1-integrins provides a clear and sufficient selective criteria that one skilled in the art may use together with some routing screening to identify all claimed antagonists, including antibodies, oligonucleotides, peptides, and organic molecules (page 8, lines 6-9).

Additionally, the specification explains that a number of conventional screening methods can be used to identify antagonists with required specificity. Such screening methods are described for identification of antibodies (pages 12-14), peptides (pages 15-16) and other antagonists (pages 17-18). The specification further teaches that antagonists of the present invention may be identified by a binding assay (pages 18-19) and may be further screened by an angiogenesis assay (pages 19 – 21).

Also, the specification provides a specific example of using the general methods and criteria set forth in the instant specification to arrive at the monoclonal antibody FM155. This antibody modifies binding of MMP-9 to β1 integrin and, thus, satisfies the requirements of claim 1.

Considering the routine art-recognized methods of making target-specific antigens, fully characterized target (binding site of MMP-9 and β1 antigen), the specific example of such antigens (FM155 antibody), one of skill in the art would have recognized that applicants were in possession of the claimed antigens at the time the application was filed. Therefore, the rejection of claims 1, 5, 6, 8-17, and 22-24 under 35 U.S.C. 112, first paragraph, should be withdrawn.

Rejection Under 35 U.S.C. § 103(a):

The Examiner sustained the rejection of claims 1-14, 17, 22-24, and 105-106 under 35 U.S.C. § 103(a) as being unpatentable over Melvin *et al.* (WO 97/00449, January 1997 (Melvin)) in combination with Newton *et al.*, Int'l. Jnl. Oncol., Vol. 6, pages 1063-1070, 1995 (Newton). The Examiner continues to argue that it would

be obvious to combine Melvin and Newton because Melvin "anticipates antagonists that directly ***inhibit the activity of proteolytic enzymes*** (e.g. MMP-9), which can be used to inhibit a disease state as cancer," and "Newton teaches ***antagonists of integrins*** that are useful for inhibiting metastasis of tumor cells." Based on these teachings, the Examiner concludes that prior art suggests "antagonists that modify the interactions between proteolytic enzymes and integrins." Applicants respectfully disagree. This rejection is mute with respect to the canceled claims 2-4, 7, 105, and 106. With respect to the claims 1, 5-6, 8-14, 17, 22, and 24, the rejection is traversed.

There is ***no suggestion in either of the cited references of modifying the antigens disclosed therein in the direction of the present invention***, nor is there any suggestion whatsoever of the desirability of such a modification. Amended claim 1 is directed to an antagonist that ***modifies interaction between MMP-9 and β1-containing integrin***. But neither Melvin nor Newton teaches or suggests binding of MMPs and integrins, much less antigens modifying such binding.

Melvin does not teach or suggests an antagonist affecting binding of MMP-9 to a β1-containing integrin. Melvin ***generally describes preventing activation of MMPs*** by "blocking access of substrates or cofactors to catalytic sites on the enzyme, by altering enzyme conformation or by mimicking the peptide which is cleaved from the pro-enzyme, by reproducing the action of TIMPs, by blocking binding to the tumor cell surface, ... by inhibition of the MMP catalytic sites" (p.4, line 34 – p.5, line 5), or "bind[ing] to the zinc atom at the active site" (p.3, lines 22-22). Although Melvin mentions inactivation of catalytic cites of MMPs, he specifically describes inactivation ***of zinc catalytic site*** only, which is not involved in binding of integrins to MMP..

Also, Melvin generally states that ***MMPs are capable of degrading extracellular matrix or interstitial connective tissue*** (page 1, lines 18-27 and lines 33-35). The extracellular matrix includes three classes of proteins: (1)

structural proteins, such as collagen and elastin, (2) specialized proteins, such as fibrillin, fibronectin, and laminin, and (3) proteoglycans. None of these proteins are integrins. Melvin does not describe any other substrates of MMPs, much less transmembrane proteins, such as integrins.

Even if teachings of Melvin were interpreted to be directed to any antagonist inhibiting any catalytic site of the MMP, still it would not have been obvious to those skilled in the art to arrive at the instant claim 1, which requires an antagonist modifying interactions between MMP-9 and β1-containing integrin. At best, Melvin, discloses a genus of antigens, of which the antigen of claim 1 is, arguably, a species. The genus disclosed in Melvin is very large. The presently claimed antigen that modifies binding of MMP-9 and β1-containing integrin is only one type of many possible types of antigens. It is well-established, that a prior genus does not render a later species claim unpatentable under §103 if it is demonstrated that the particular species claimed has unique and unexpected advantages or properties that distinguish it from other species within the prior genus. *In re Baird*, 16 F.3d 380, 383 (Fed. Cir. 1994); *In re Lemin*, 332 F.2d 839 (C.C.P.A. 1964) ("Generally speaking, there is nothing unobvious in choosing 'some' among 'many' indiscriminately. . . . Here, however, the choice is based on a discovery by Lemin that some compounds, falling within a prior art genus have a special significance.").

The presently claimed antigen has such "special significance." As explained in the applicants' previous response, prior to the present invention, it ***was not known or expected in the art that proteolytic enzymes, such as MMPs, may bind directly to integrins*** and that a modification of an interaction between a proteolytic enzyme and an integrin may inhibit angiogenesis and/or tumor growth. Thus, a mere description of MMPs and their well-known substrates, such as basement membrane and interstitial connective tissue of extracellular matrix,

without a description of MMP binding to integrins and antagonists inhibiting such binding, would not have made the present invention obvious.

Similarly to Melvin, **Newton** fails to teach or suggests antigens that modify interaction between MMP-9 and β1-containing integrins. Newton teaches an antigen that inhibits metastasis of breast carcinoma cells by ***binding to the $\alpha_5\beta_1$ integrin and inhibiting its interaction with fibronectin***, a protein of extracellular matrix. Newton does not describe a binding of integrins to any other molecules, much less MMPs.

Unlike the present invention that focuses on interaction of β1-containing integrins ***with MMPs*** to inhibit angiogenesis and growth of tumors, Newton teaches importance of blocking interaction of $\alpha_5\beta_1$ integrin and ***fibronectin*** to inhibit metastasis (Abstract). The description of interaction between $\alpha_5\beta_1$ integrin and fibronectin, without a description of direct binding of MMPs to β_1-containing integrin and antagonists inhibiting such binding, would not have made the present invention obvious.

It is well-known in the art that biomolecules have ***numerous binding sites*** with different affinities and 3-D configurations. The binding site of MMP-9 to proteins of extracellular matrix are likely to be completely different from that for binding integrins. In fact, as it was discussed in the applicants' previous response, an antagonist obtained in accordance with the teachings of the present invention (FRIP-1, CRLRSGEPQC) is quite different from antagonists of Melvin (SSFGFRTVKH; TSLGLPPDVQRVD, and KLGLGADVAQVT)[1]. Thus, based on the teachings of Melvin and Newton, those skilled in the art would not have found it to

[1] Applicants would like to note that the reference to FRIP-1 above is intended only as evidence of different binding sites in MMPs associated with the binding of integrins and proteins of extracellular matrix. It is not Applicants' intention to limit the claims to FRIP-1.

be obvious to modify Melvin by raising antibodies with the specificity to the binding site of MMP to β1- containing integrin instead of the binding site of MMP to a protein of extracellular matrix.

In summary, Melvin describes interaction of ***MMPs with proteins of extracellular matrix***, such as collagen, elastin, fibrillin, fibronectin, laminin, and proteoglycans. Melvin, however, fails to teach interaction of MMPs with any other substrates such as integrins. Newton describes interaction of ***$\alpha_5\beta_1$ integrin and fibronectin***, but fails to teach interaction of integrins with any other molecules, such as MMPs. Thus, applicants respectfully submit that neither Melvin nor Newton provide a suggestion for antagonists that modify interactions between MMP-9 and β1-containing integrins. Therefore, claim 1 and its dependent claims 5-6, 8-14, 17, 22, and 24 are patentable over a combination of Melvin and Newton references.

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the **applicants request a telephone interview with the Examiner** to discuss the steps necessary for placing the application in condition for allowance. The undersigned attorney can be reached at (213) 337-6853.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
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